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12. (Amended) The method of claim 11, wherein said matrix metalloproteinase inhibitor is doxycycline.

A2 Cont

13. (Amended) The method of claim 12, wherein 15 mg/kg of said doxycycline is administered twice daily.

14. (Amended) The method of claim 11, wherein said matrix metalloproteinase inhibitor is 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid.

16. (Amended) A method for prophylaxis or treating chemotherapy or radiation induced liver disease comprising administering 15 mg/kg of doxycycline twice daily.

A3

17. (Amended) A method for prophylaxis or treating chemotherapy or radiation induced liver disease comprising administering 100-200 mg/hour of 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid.

Attached hereto is a marked-up version of the changes made to the claims. The attached pages are captioned "Version with Markings to Show Changes Made".

REMARKS

Claims 1 to 17 are pending in the subject application. By this Amendment and Response, claims 1 to 7, 9 to 14, and 16 to 17 have been amended. The amendments to the claims are not intended to be a disclaimer or dedication to the public of the subject matter of the claims as previously presented. Support for the amendment is found in the application as filed and no new matter has been added. Entry of these amendments is respectfully requested.

In view of the preceding amendments and the remarks that follow, reconsideration and withdrawal of the objections and rejections are respectfully requested.

CLAIM OBJECTIONS

Claims 1-2 and 11 were objected to because of the informal use of the parenthetical expressions "SOS" and "MMP". Applicants have corrected the claims to eliminate the use of the term abbreviations and respectfully request that the Examiner withdraw his objections.

Claim Rejections – U.S.C. § 112, First and Second Paragraphs

Claims 1-6, 11-13 and 16 stand rejected under 35 U.S.C. § 112, first and second paragraphs on the grounds that the claims contain subject matter that was not described in the specification so as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention and for being indefinite and failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office remarked that the MMP inhibitor "doyxycycline" was not supported in the specification and that it is not clear what "doyxycycline" is.

Applicant has amended claims 1-6, 11-13 and 16 to correct the misspelling of "doyxcycline" with the proper spelling of "doxycycline". In light of this technical correction, Applicant respectfully requests reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. § 112, first and second paragraphs.

Claims 1-17 stand rejected under 25 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The the term "preventing" in claims 1-17 has been amended to recite "prophylaxis" and, therefore, the rejection of claims 1-17 should be withdrawn.

With respect to claim 10, because the terms are unique numeric designations that describe the chemicals recited, a person skilled in the art would be able to identify the recited compounds. Therefore, these numeric designations are not indefinite. For convenience, Applicant has replaced the numeric designations CGS 27023 A and Ro 27023 with the chemical formulas (N-hydroxy-2(R)-[[4-methoxysulfonl](3-picolyl) amino]-3-methylbuteamide hydrochloride) monohydrate and (3(R)-(cyclopentylmethyl)-2(R)-[(3,4,4-trimethyl-2,5-dioxo-1- imidazolidinyl)methyl]-4-oxo-4-piperidinobutyrohydroxamic acid) respectively. Therefore, the rejection of claim 10 should be withdrawn.

In view of the preceding remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first and second paragraphs, are respectfully requested.

Claim Rejections – 35 U.S.C. § 102

Claims 1-5, 9, and 11-12 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Periostat (doxycycline capsules)(the "Periostat reference"). The Examiner alleged that Periostat teaches twice a day administration of doxycycline to adult patients.

Applicants respectfully traverse.

For a prior art reference to anticipate under 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference. See, Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. See, Structural Rubber Prods. Co. v. Park Rubber Co., 749 F.2d 707, 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984). Furthermore, to constitute an anticipatory reference, the prior art must contain an enabling disclosure. See, Chester v. Miller, 906 F.2d 1574, 1576, n.2, 15 U.S.P.Q.2d 1333, 1336, n. 2 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself, and thereby the public, in possession of the invention. See, In re Donohue, 766 F.2d 531, 533, 226 U.S.P.Q.2d 619, 621 (Fed. Cir. 1985).

The Examiner states that the Periostat reference teaches a twice a day administration of doxycycline to adult patients. However, the Examiner omits the fact that the Periostat reference discloses that the administration of doxycycline hyclate in conjunction with scaling and root planing to treat periodonatal disease. Because of these additional required elements disclosed in the Periostat reference, the claimed invention, which does not require the steps of scaling or root planing, is not enabled. A person of ordinary skill in treating patients with side effects from chemotherapy and radiation therapy would not have been able to combine the description in the Periostat reference for treating periodontal disease and placed himself in possession of the invention. Because the Periostat reference is not enabling, it does not anticipate claims 1-5, 9, and 11-12.

Claim 10 was also rejected under 35 U.S.C. § 102(b) as allegedly anticipated by McKearn et al. (WO 00/38717)(the "McKearn reference"). The Examiner stated that the McKearn reference "teaches a method comprising employing matrix metalloproteinase inhibitor in combination with radiation therapy" and that it further teaches the following matrix metalloproteinase inhibitors specifically: Marimastat, Metastat, Bay-12-9566 and D-2163. Claim 10 is dependent from claim 1 and therefore incorporates every element of claim 1 into it. Because the Examiner did not find that the McKearn reference anticipated claim 1, it cannot be found to anticipate dependent claim 10. Applicants respectfully request reconsideration and withdrawal of the rejection.

In view of the preceding remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1-6, 11-13, and 16 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the Periostat reference. The Examiner stated that the Periostat reference teaches the administration of 20 mg twice a day of doxycycline to adult patients and that it would have been obvious to one of ordinary skill to administer 15 mg of doxycycline twice a day.

Applicant respectfully traverses.

The U.S. Court of Appeals for the Federal Circuit held that "[t]he PTO has the burden under section 103 to establish a *prima facie* case of obviousness . . . It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 1074 (Fed Cir. 1988). *Prima facie* obvious is met when: (1) there is some suggestion or motivation to modify the reference; (2) there is a reasonable expectation of success; and (3) the prior art reference teaches or suggests all the claim limitations. *See, In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) cited in MPEP §§ 2142, 2143. The Office does not establish a *prima facie* case of obviousness with the Periostat reference as not one of the criteria for prima facie obviousness is met.

The Periostat reference discloses the treatment of periodonatal disease with doxycycline. There is no motivation or suggestion within the Periostat reference to modify the recommended periodontal treatment to liver disease conditions. There was certainly no expectation of success that the application of a treatment for periodontal disease to a patient suffering from liver disease would successfully alleviate the patient's condition. And as discussed above with regards to the 35 U.S.C. § 102 rejection, the Periostat reference does not enable or teach all the claim limitations. Applicant respectfully submits that claims Claims 1-6, 11-13, and 16 are in condition for allowance.

Claims 4, 7-10, 14-15 and 17 are also rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the McKearn reference and Watanabe et al. (USPN 6,150,394) ("the Watanabe reference"). The Office stated that the McKearn reference teaches a method comprising employing matrix metalloproteinase inhibitor in combination with radiation therapy. The Office further opined that the Watanabe reference teaches a method of administering, including parenterally, 0.01

mg/kg/day to 100 mg/kg/day of compositions matrix metalloproteinase inhibitors. Taken together, the Examiner argued, one of ordinary skill in the art would have been motivated to administer 100-200 mg/hour of 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid to the patient.

Applicant respectfully traverse.

None of the criteria for prima facie obviousness is met with the combination of these two references. The references do not teach the invention of the claims as noted above. Additionally, there is no motivation to combine the two references. McKearn teaches the administration of MMP inhibitors and radiation to treat cancer. The claimed invention is not used to treat cancer, but rather is administered to treat the side-effects of radiation and chemotherapy. Nothing in Watanabe suggests or creates a motivation to combine the references for the treatment of radiation-induced liver disease. Both the McKearn and the Watanabe references involve the treatment using 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid in combination with other treatments such as radiation or as part of a formula with other active ingredients. The claimed references do not establish an expectation that the administration of 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid would be effective alone. The claimed invention, however, discloses the administration of MMP without the assistance of other active ingredients. Finally, the McKearn and Watanabe references do not disclose every element of the claimed invention. Neither reference discloses the administration of matrix metalloproteinase inhibitors for the treatment of chemotherapy or radiation-induced liver disease. The combination of McKearn and Watanabe do not establish a case of *prima facie* obviousness.

In view of the preceding remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 is respectfully requested.

CONCLUSION

For the reasons set forth above, it is believed that all claims present in the application are in condition for allowance. Therefore, it is requested that this application be passed to allowance. However, if an appropriate payment does not accompany or precede this submission, the Commissioner is hereby authorized to charge any fees required under 37 C.F.R. § § 1.16 and 1.17, including fees for any petition for extension of time, or credit any overpayment to Deposit Account No. 50-1192.

If the Examiner has any questions or would like to discuss this Amendment, please do not hesitate to contact the undersigned at the telephone number below.

Please address all correspondence regarding this communication to the following address:

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Respectfully submitted,

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1. (Amended) A method for ~~preventing~~prophylaxis or treating Sinusoidal Obstruction Syndrome ~~("SOS")~~ comprising administering a matrix metalloproteinase ~~("MMP")~~ inhibitor.

2. (Amended) A method for ~~preventing~~prophylaxis or treating chemotherapy- or radiation-induced liver disease comprising administering a matrix metalloproteinase ~~("MMP")~~ inhibitor.

3. (Amended) The method of claim 2, wherein said chemotherapy-induced liver disease includes ~~SOS~~Sinusoidal Obstruction Syndrome, nodular regenerative hyperplasia, peliosis hepatis, immunosuppression-induced hepatic venoocclusive disease, and sinusoidal dilatation.

4. (Amended) The method of claims 1 or 2, wherein said ~~MMP~~matrix metalloproteinase inhibitor is ~~doyxcycline~~doxycycline or 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid.

5. (Amended) The method of claim 4, wherein said ~~MMP~~matrix metalloproteinase inhibitor is ~~doyxcycline~~doxycycline.

6. (Amended) The method of claim 5 wherein 15 mg/kg of said ~~doyxcycline~~doxycycline is administered twice daily.

7. (Amended) The method of claim 4, wherein said ~~MMP~~matrix metalloproteinase inhibitor is 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid.

9. (Amended) The method of claims 1 or 2 wherein said ~~MMP~~matrix metalloproteinase inhibitor is administered for up to 4 weeks.

10. (Amended) The ~~method~~methods of claims 1 or ~~2,~~2 wherein said ~~MMP~~matrix metalloproteinase inhibitor is Marimastat, Prinomastat, ~~RS~~(N-~~130,830, CGS 27023A~~hydroxy-2(R)-[[4-methoxysulfonl](3-picolyl) amino]-3-methylbuteamide hydrochloride) monohydrate, Solimastat, ~~BAY 12~~(3(R)-~~9566, Ro 32~~(cyclopentylmethyl)-~~3555, BMS~~2(R)-~~272591,~~[(3,4,4-trimethyl-2,5-dioxo-1- imidazolidinyl)methyl]-4-oxo-4-piperidinobutyrohydroxamic acid), Ilomastat, ~~D2163,~~ Metastat, Neovastat, or Periostat.

11. (Amended) A method for ~~preventing~~prophylaxis or treating chemotherapy or radiation induced liver disease comprising administering an effective dose of a matrix

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metalloproteinase ~~("MMP")~~ inhibitor selected from ~~doyxcycline~~doxycycline or 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid.

12. (Amended) The method of claim 11, wherein said ~~MMP~~matrix metalloproteinase inhibitor is ~~doyxcycline~~doxycycline.

13. (Amended) The method of claim 12, wherein 15 mg/kg of said ~~doyxcycline~~doxycycline is administered twice daily.

14. (Amended) The method of claim 11, wherein said ~~MMP~~matrix metalloproteinase inhibitor is 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid.

16. (Amended) A method for ~~preventing~~prophylaxis or treating chemotherapy or radiation induced liver disease comprising administering 15 mg/kg of ~~doyxcycline~~doxycycline twice daily.

17. (Amended) A method for ~~preventing~~prophylaxis or treating chemotherapy or radiation induced liver disease comprising administering 100-200 mg/hour of 2-[(4-biphenylsulfonyl)amino]-3-phenyl-propionic acid.